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Rapid Construction of the ABC Ring System in the *Daphniphyllum* Alkaloid Daphniyunnine C

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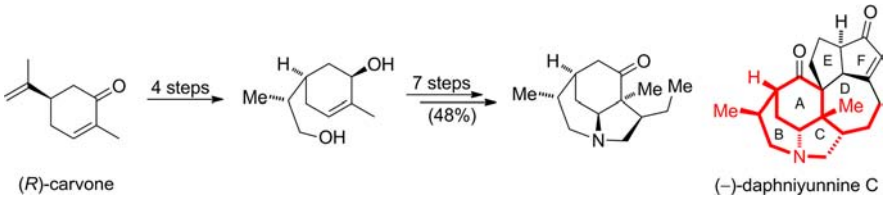
ABSTRACT



An efficient and scalable synthesis of the ABC ring system common to the calyciphylline A-type alkaloids has been developed. The tricyclic core of the alkaloids features a bowl-shaped [6−6−5] skeleton with five stereogenic centers including an all-carbon quaternary center. It was constructed rapidly from a readily available carvone derivative through a seven-step sequence involving an aza-Michael addition and Pd-catalyzed enolate α-vinylation as key steps.

The *Daphniphyllum* alkaloids are a group of highly complex polycyclic alkaloids with remarkable structural diversity (Figure 1). More than 200 family members have been isolated over the past 50 years, and they exhibit a vast collection of novel skeletons with unusual ring systems.[1] Historically, the unique structural features and intriguing biosynthesis of these alkaloids have inspired a variety of innovative and elegant studies in total synthesis.[2] One milestone that is well-recognized among organic chemists is Heathcock's biomimetic synthesis of dihydro-*proto*-daphniphylline (**1**, Figure 1) and other structurally related members based on his biogenetic proposal.[2b−d] In recent years, discoveries of unprecedented structures in this alkaloid family have continuously prompted synthetic investigations in this field.[3]

Among the >20 subgroups of the *Daphniphyllum* alkaloids, we are particularly interested in calyciphylline A-type alkaloids (Figure 2).[4] Intrigued by the synthetic challenge posed by these structures, we started a program to study the total synthesis of calyciphylline A-type alkaloids and to explore the possible formation of the core structures in other subgroup members through elaboration of their tricyclic ABC ring system. To achieve these goals, it was necessary to develop an efficient and scalable synthesis for the rapid construction of the tricyclic bowl-shaped [6−6−5] skeleton.

(1) For a review on the *Daphniphyllum* alkaloids, see: Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936–962.

(2) For the first total synthesis of a *Daphniphyllum* alkaloid, see: (a) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650–5651. For selected biomimetic syntheses, see: (b) Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734–8736. (c) Piettre, S.; Heathcock, C. H. *Science* **1990**, *248*, 1532–1534. (d) Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2554–2566.

(3) For selected recent synthetic approaches on *Daphniphyllum* alkaloids, see: (a) Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593–605. (b) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833–1836. (c) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658–5661. (d) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267–1269. (e) Bélanger, G.; Boudreault, J.; Lévesque, F. *Org. Lett.* **2011**, *13*, 6204–6207. (f) Coldham, I.; Watson, L.; Adams, H.; Martin, N. G. *J. Org. Chem.* **2011**, *76*, 2360–2366. (g) Weiss, M. E.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501–11505.

(4) For recent synthetic approaches to calyciphylline A-type alkaloids, see: (a) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461–5464. (b) Xu, C.; Liu, Z.; Wang, H.; Zhang, B.; Xiang, Z.; Hao, X.; Wang, D. Z. *Org. Lett.* **2011**, *13*, 1812–1815. (c) Sladojevich, F.; Michaelides, I. N.; Darses, B.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 5132–5135. (d) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684–1687. (e) Xu, C.; Wang, L.; Hao, X.; Wang, D. Z. *J. Org. Chem.* **2012**, *77*, 6307–6313. (f) Feng, B.; Zheng, H.; Zhao, C.; Jing, P.; Li, H.; Xie, X.; She, X. *J. Org. Chem.* **2012**, *77*, 8367–8373. (g) Yang, M.; Wang, L.; He, Z.-H.; Wang, S.-H.; Zhang, S.-Y.; Tu, Y.-Q.; Zhang, F.-M. *Org. Lett.* **2012**, *14*, 5114–5117.

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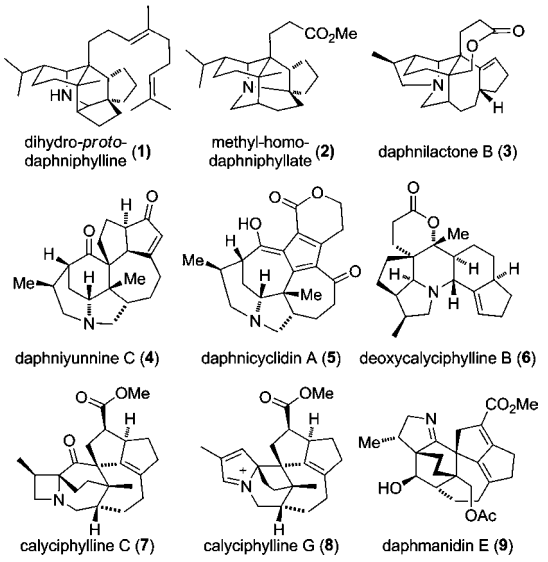


Figure 1. Structural diversities of the *Daphniphyllum* alkaloids.

Our synthetic plan is illustrated in Scheme 1, with daphniyunnine C (**4**, Figure 1) as an exemplary target.[5] We envisioned that bond disconnections involving an intramolecular Pauson–Khand reaction[6] could greatly simplify the hexacyclic molecule into the less complicated tetracyclic structure **16**. This key spiro intermediate could be formed from **17** using a ring-closing metathesis (RCM) strategy,[7] which in turn could be procured through a kinetic alkylation of the unsaturated ketone in **18**. We reasoned that the stereochemistry of this step could be tightly controlled by the bowl-shaped architecture of the substrate **18**. A short sequence from (*S*)-carvone (**23**) was

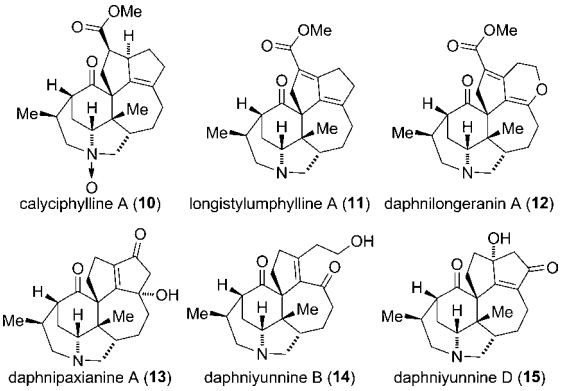
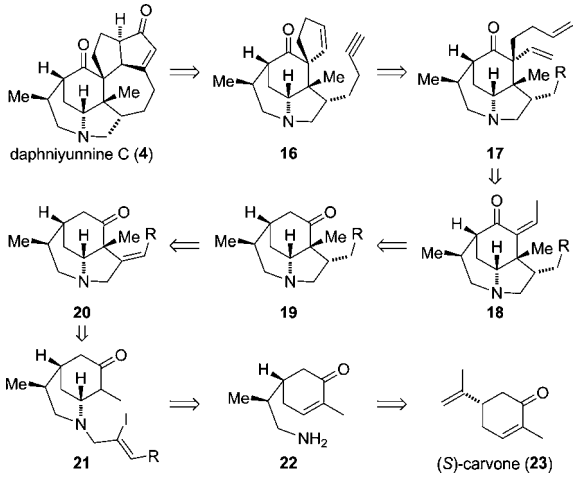


Figure 2. Representative calyciphylline A-type alkaloids.

Scheme 1. Retrosynthetic Analysis of Daphniyunnine C



expected to readily establish all the stereogenic centers in **18**. An intramolecular aza-Michael addition of carvone derivative **22** followed by alkylation and subsequent Pd-catalyzed enolate α-vinylation reaction[8] could generate **20**. Hydrogenation from the convex side of **20** would transform this substrate to the tricyclic product **19** with five stereogenic centers in place.

Herein, we report our success in the facile construction of the common bowl-shaped [6−6−5] skeleton **32** in calyciphylline A-type alkaloids with five stereogenic centers (Scheme 2) from the cost-effective (*R*)-carvone.

Our synthesis took advantage of a known transformation from (*S*)-carvone (**23**) to *ent*-**24** reported by Overman and co-workers.[9] This four-step sequence is very robust and can be readily scaled up to produce over 10 g of **24** in one batch. This transformation neatly controlled the required stereochemistry of the methyl substituent on the B ring. With a sufficient supply of **24** in hand, we started to

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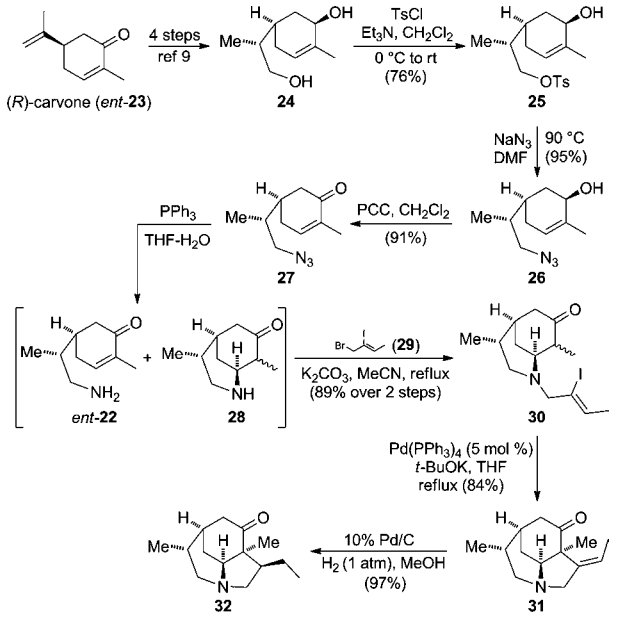
(7) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800–3801. (b) For a review on the application of metathesis reactions in total synthesis, see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.

(8) For applications of Pd-catalyzed enolate α-vinylation reactions, see: (a) Piers, E.; Oballa, R. M. *Tetrahedron Lett.* **1995**, *36*, 5857–5860. (b) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057–2059. (c) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225–2228. (d) Zhao, S.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 687–690. (e) Cao, H.; Yu, J.; Wearing, X. Z.; Zhang, C.; Liu, X.; Deschamps, J.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 8013–8017. (f) Solé, D.; Diaba, F.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746–5749. (g) Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippin-Anderson, J.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 7565–7581. (h) Zhao, S.; Liao, X.; Cook, J. M. *Org. Lett.* **2004**, *6*, 249–252. (i) Yu, J.; Wearing, X.; Cook, J. M. *J. Org. Chem.* **2005**, *70*, 3963–3979. (j) Zhou, H.; Liao, X. B.-W.; Yin, Y.; Ma, J.; Cook, J. M. *J. Org. Chem.* **2006**, *71*, 251–259. (k) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377. (l) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3618–3621. (m) For a model study of applying the Pd-catalyzed enolate α-vinylation reaction in the construction of the B ring in calyciphylline A, see ref 4a.

(9) (a) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650–6652. (b) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *74*, 5458–5470.

Scheme 2. Synthesis of [6−6−5] Tricyclic Skeleton **32**



explore our synthetic strategy by substitution of the hydroxyl group with an amino group. The primary hydroxyl group in **24** was selectively activated as a tosylate, which underwent nucleophilic substitution with sodium azide to afford **26** in excellent yield. Oxidation of the allylic alcohol with PCC[10] and a subsequent Staudinger reaction[11] produced a mixture of *ent*-**22** and the aza-Michael addition product **28**. With no need for purification, the mixture was directly treated with allyl bromide **29**[8f] under typical alkylation conditions to generate a pair of diastereomers **30**. In this step, owing to the intrinsic structural feature of the substrate, the aza-Michael addition could only occur from one face of the Michael acceptor and neatly install the C−N bond in a stereoselective manner on the A ring. Because the diastereomeric center in **30** would be lost in the next step, the mixture was used without separation. When **30** was treated under typical conditions for Pd-catalyzed enolate α-vinylation, it was smoothly converted to the tricyclic product **31** with a newly formed all-carbon quaternary center in 84% yield. Again, the intrinsic concavity of the substrate facilitated the stereoselective formation of the challenging all-carbon quaternary center. As we anticipated, hydrogenation of the double bond in **31** with Pd/C afforded **32** in almost quantitative yield with absolute stereochemical control. The stereochemistry of **32** was unambiguously confirmed through single crystal X-ray crystallographic analysis of the oxalate salt of **32** (Figure 3).

(10) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647–2650.
(11) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635–646. (b) For a review on Staudinger reactions, see: Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406.

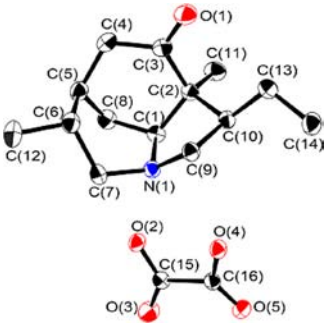


Figure 3. ORTEP depiction of the oxalate salt of **32** (thermal ellipsoids drawn at the 50% probability level).

Given that this synthetic sequence employed straightforward transformations and cost-effective chemicals and reagents in each step, it could be readily scaled up to supply sufficient material for further studies. To date, nearly 15 g of **32** have been prepared in our laboratory.

In summary, we have developed an efficient and scalable synthetic approach for the rapid construction of the ABC ring system commonly found in the *Daphniphyllum* subclass calyciphylline A-type alkaloids. By harnessing the intrinsic structural features of individual intermediates, a high degree of stereochemical control was achieved throughout the sequence. A seven-step sequence allowed us to build the rather complex tricyclic core skeleton from a readily available carvone derivative (**24**) in an overall yield of 48%. Notably, this core skeleton contains five stereogenic centers including an all-carbon quaternary center, making it a nontrivial synthetic target. Further studies toward the total synthesis of daphniyunnine C and other members of the *Daphniphyllum* alkaloids are currently underway in our laboratory.

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Supporting Information Available. Experimental details and procedures, compound characterization data, copies of ^{1}H and ^{13}C NMR spectra for new compounds, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.